**Mallory Kane Writing Samples**

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**Survival outcomes following immune checkpoint inhibitor therapy of advanced cutaneous melanoma by age and tumor infiltrating lymphocytes in the primary cutaneous site.**

**Background:** Tumor infiltrating lymphocytes (TILs) in the tumor microenvironment generate anti-tumor immunity and are associated with response to immune checkpoint inhibitor (ICI) therapy of melanoma. However, likelihood of response to ICI therapy depends upon intensity of TILs, proportion of effector and regulatory T cells and age. **Methods:** In a research study approved by the Institutional Review Board of University of Connecticut, we retrospectively analyzed outcome of patients diagnosed with cutaneous melanoma between 2009 and 2019 and developed unresectable stage III or stage IV disease requiring ICI treatment. Patients were stratified by age (< 75 and > 75 years old) and TILs at the primary cutaneous melanoma site categorized as brisk (present throughout vertical phase), non-brisk (present in one of more foci of vertical phase) or absent. Patient’s age at the time of metastases, as well as 12- month and 24-month overall survival (OS) following ICI treatment was recorded. **Results:** A total of 93 patients were screened, and 68 were included for analysis of survival outcome. Patients had to receive at least one dose of ICI treatment at UConn Health and had available data on TILs of primary cutaneous melanoma. In patients over 75 years of age, those with brisk TILs had an increased 24-month survival compared to those with non-brisk or absent TILs (100% vs. 45%, p = 0.04). In patients < 75 years of age, the 24-month survival was similar in those with brisk and non-brisk or absent TILs (67% vs. 69%, p = .91). There was no significant difference in overall survival between patients < 75 or > 75 years with brisk TILs (67% vs. 100%, p = .19). Additionally, in patients with non-brisk or absent TILs, there was no significant difference in survival between those > 75 vs < 75 years (45% vs. 69%, p = .09). **Conclusions:** Our findings suggest that intensity of TILs in primary cutaneous melanoma is predictive of outcome following ICI treatment of advanced melanoma in patients over 75 years of age. These findings support possible interaction between qualitative differences of TILs and patient age. Our findings may help identify older melanoma patients who may benefit from ICI treatment.

**A case of possible Stiff Person Syndrome (SPS) / Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM) misdiagnosed as Catatonia**

**Abstract**

Stiff person syndrome (SPS) is a rare neurological disorder manifesting as profound stiffness and rigidity. It is believed to be caused by autoantibodies against antigens involved in the synthesis and release of Gamma-aminobutyric acid (GABA) – a major inhibitory neurotransmitter of the central nervous system (CNS). Progressive encephalomyelitis with rigidity and myoclonus (PERM), also known as SPS-plus syndrome, has more extensive involvement of the CNS and autonomic nervous system. Diagnosis of SPS has become largely reliant on the detection of antibodies in the serum and CSF. However, existing literature suggests that up to one third of cases of SPS have no known antibody positivity. This case report describes a presentation of presumed antibody negative SPS which was initially misdiagnosed as catatonia. It aims to highlight the need for improved diagnostic criteria and increased recognition of SPS, as many patients with this syndrome live disabled for years before they are diagnosed and treated.

* 1. **Introduction**

First described at the Mayo Clinic in 1956, Stiff Person Syndrome (SPS) is a rare neurological disorder with an estimated prevalence of 1-2 per million [1]. The condition is believed to be autoimmune in nature, thus concomitant autoimmune diseases are common [2]. The etiology of SPS is thought to be due to impaired muscle relaxation due to formation of autoantibodies against antigens involved in the synthesis and release of Gamma-aminobutyric acid (GABA) – a major inhibitory neurotransmitter in the central nervous system (CNS) [2]. Glutamic acid decarboxylase (GAD), an enzyme that transforms glutamate into GABA, is currently the most identified antigen target in SPS [2, 3]. Anti-GAD antibodies have been identified in up to 80% of cases [3]. Anti-glycine antibodies are the second most common antibodies in SPS seen in 20% of patients, and less commonly, anti-amphiphysin, anti-gephyrin, anti-smooth muscle, anti-islet cell, and anti-thyrogastric antibodies [4 - 6]. Approximately 1/3 of cases of SPS reported in the literature have no antibody positivity [2]. Anti-glycine receptors (anti-GlyR antibodies) have been noted in clinical variants of SPS, especially in progressive encephalomyelitis with rigidity and myoclonus (PERM). Also known as SPS-plus syndrome, PERM presents with hyperintense signals of the spinal cord and brainstem on magnetic resonance imaging (MRI), indicating more extensive involvement of the CNS and autonomic system [7].

SPS presents insidiously with progressive rigidity of the trunk and axial muscles. The clinical diagnostic criteria for classic SPS includes stiffness in the limb and axial muscles, painful spasms, evidence of continuous motor activity in agonist and antagonist muscles demonstrated by electromyography (EMG), absence of other neurological impairments that could support an alternative diagnosis, positive serology for anti-GAD antibodies at a level > 10,000 IU/mL, and clinical response to therapy with benzodiazepines [1]. The treatment for SPS includes benzodiazepines and intravenous immunoglobulin (IVIG) [8].

Patients with SPS often present with comorbid, nonspecific psychiatric symptoms, leading to challenges in diagnosis and delays in adequate treatment. In case reports, SPS has often been misdiagnosed as conversion disorder, psychogenic movement disorder, panic disorder or anxiety disorder [2].

Here we describe a case report in which a patient was admitted to the hospital with altered mental status and progressively became increasingly rigid. Three separate admissions and 38 days of inpatient hospitalization passed since the start of symptoms before a diagnosis of stiff person syndrome was raised and treatment was initiated. In telling this patient’s story, we aim to highlight an uncommon presentation of this rare disorder and illuminate the importance of considering SPS as a diagnosis even in absence of the classic anti-GAD antibodies. Increasing awareness of SPS will help the condition to be recognized more promptly. Early detection may prevent permanent neurological deficits or other complications such as rhabdomyolysis that come with delay in diagnosis and treatment.

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**The Power of eConsults: comparing safe long-term opioid (LTOT) prescribing and pain management plan characteristics amongst patients who were mandated to receive chronic pain eConsult versus those who were requested by the treating prescriber at UCONN Health.**

**Background:**

In 2021, over 106,000 people died from illicit and prescription opioid overdose in the United States [1]. Prescription opioid death rates rose from 3,442 deaths in 1999 to 16,706 in 2021 [1]. There have been several nation-wide policy changes, new state laws, and initiatives to combat this marked rise in prescription associated opioid overdose, such as the use of state prescription drug monitoring programs, medication agreements for treatment plans, naloxone distribution, random urine screening, and consistent clinical follow up mirroring other chronic conditions [2]. At UCONN Health, pain management e-consults have been implemented by an interdisciplinary team consisting of an addiction psychiatrist, pharmacist, and two primary care physicians (PCP) to enhance quality of life, reduce pain, and optimize medication regimens to mitigate risk of overdose and adverse effects. These consults are provided at PCPs’ request (referred consults) as well as implemented for safety for patients on high-risk medication regimens based on morphine milligram equivalents (MME) > 90 or those who have missed follow up appointments in the past 6 months (mandated consults). The goal of this study was to evaluate if the origin of reason for eConsult affected the uptake of recommendations and improvement in safety metrics for high-risk patients on LTOT.

**Methods:**

All eConsults conducted at UCONN Health between 2019 - 2022 (n= 117) for patients followed by our primary care physicians were reviewed and categorized as mandated (consult prompted by MME > 90 or lack of follow up in the previous 6 months, n=46) or referred (consult prompted by PCP referral, n=71). Outcomes in mandated and referred patients were compared at 3-, 6-, and 12-months after initial eConsult to determine if there was a difference in percentage of recommendations followed in regards to institutional LTOT quality care metrics including: MME, medication agreement use, quarterly follow up appointments, urine toxicology screening at 6-month intervals, and naloxone prescriptions. In addition, eConsult acceptance was followed concerning: opioid prescribing, controlled non-opioid prescribing, non-controlled medication, and non-pharmaceutical (imaging, lab tests, referrals) recommendations. Patients lost to follow up at the 3-month mark (n=4) were excluded as there was no single time point of data however all other patients lost to follow up (who had at least the 3-month follow up data points) were carried forward using the last observed data points. Specialty (orthopedics, oncology, surgery, etc.), one-time, or outside the health system eConsults (n=4) were excluded from data analysis due to lack of access to data (outside consults) and lack of primary pain management responsibilities (specialty consults).

**Results:**

At baseline, average MME for referred eConsults was 135 and mandated was 106. 12 months after initial eConsult, referred consults MME was 87 (declined by 48) and mandated was 89 (declined by 17). At the 12-month mark, percent of opioid recommendations followed in referred eConsults was 51% compared to 41% in mandated eConsults. The percent of controlled substance non-opioid recommendations steadily increased at 3-,6-, and 12-month follow up appointments in mandated patients (25%, 29%, 31%) and referred patients (38%, 47%, 55%). At the 12-month mark, percent of non-opioid, non-controlled recommendations followed in referred eConsults was 70% compared to 62% in mandated eConsults. Percentage of patients using a medication agreement at 12 months increased 19% (64 to 83%) in mandated eConsults and 13% (53% to 66%) in referred eConsult patients. Percentage of patients agreeable to urine toxicology screening increased from 31% to 37% over 12 months in mandated consults but did not improve in referred patients (51% at baseline, 48% in 12 months). Naloxone prescription recommendations decreased overtime in mandated consults (29% at baseline, 20% at 12 months) and referred consults (28% at baseline, 27% at 12 months).

**Conclusions:**

The percentage of patients following opioid, controlled non-opioid, and non-controlled pharmacologic recommendations steadily increased overtime at the 6- and 12-month follow up appointments indicating that e-consults are effective in initiating change and that behavioral change can take time. Medication agreement use also substantially increased overtime after eConsult in both groups. However, adherence to urine toxicology screening and naloxone prescription recommendations appear to be more difficult to improve with e-consult. Both mandated and referred consults had a decline in MME overtime and an MME < 90 at the 12-month follow up, which is an important safety cut off for opioid use.

**Implications**

Overall, our study suggests that both mandated and referred eConsult methods are effective in improving chronic pain regiments, lowering MME, and increasing medication agreement adherence. Our data suggests that adjustment in approach may be needed to increase adherence to urine toxicology screening and naloxone from e-Consults.

**Hot Bed**

The first time I administered naloxone, I was shaking in fear. It was a frosty morning, so early the stars were out instead of the sun, and I was working in the emergency department. Our patient arrived barefoot and barely breathing, only the whites of his eyes visible past his droopy tattooed lids. I braced myself as Naloxone filled his nostrils, anticipating violence as I transformed his deadly bliss into aggressive withdrawal. But instead of ferocity, I was met with uneventful silence as he regained consciousness. I helped him change out of his cold, wet jeans and into a pair of ciel blue scrub pants, wrapped him in a warm blanket and left the room.

The second time I Narcan-ed someone, it was a familiar face. Eighteen hours had passed, but I was still working the same shift. A new set of first responders wheeled a patient into the trauma bay. Only a few seconds passed before I noticed the tattooed eyelids and ciel blue scrub pants. Confused, I looked to the paramedic who explained that the patient snuck out of the emergency department, making it only one block away before overdosing on the sidewalk.

Substances flood the halls of our emergency department. I work in an inner-city hospital located on a fentanyl hot bed. It’s not unusual for me to step on empty dime-bags as I walk from the parking garage to the front door. Our patient population is a dichotomy of drug-users and non-drug-users. After just two weeks working here, I got to know the regulars. A pleasant 23-year-old girl with arms covered in track marks and fingernails wedged with dirt. She comes in multiple times a week with somatic complaints that always resolve after I give her a turkey sandwich. A 70-year-old man with a failing liver and inability to put down the bottle of Jack who repeatedly presents seizing in withdrawal. A pregnant woman with a crack addiction and compulsive need to assess her baby’s vitality after using. When I send off the regulars, I tell them that I hope I don’t see them again. Not because I don’t want to help. I say this because I care, because I want them to heal and find the right path. Yet, when their attendance fizzles, I carry sadness knowing that it likely symbolizes another loss to addiction rather than growth and redirection.

The patients who stick with me most are not the regulars. They are the one-timers. Those whose lives are abruptly unplugged, ceased by substance. I often think of Quinn, a 13-year-old whose heart stopped beating after she smoked her mom’s marijuana which was laced with fentanyl. Mason, a 35-year-old with so much cocaine coursing through his veins that his aorta ruptured, leading him to bleed to death internally. I think of Xavier, a 23-year-old who drank a pint of vodka and drove 70 mph into a tree.

When it comes to substance use, I often see people at their lowest points. I try to focus on the immediate issues, knowing I can’t solve the big ones. I hand out subpar hospital food, homeless shelter pamphlets, directions to non-profits that provide clean needles. I do what I can. Yet, this fight often feels futile. According to my patients, fentanyl can be purchased at just about any corner grocery store in town for a low price of three dollars a bag. It is easy to get. More and more people around me find their way to substance and struggle to find their way out.

One of the biggest barriers of progress in the battle against addiction is stigma. Many users struggle secretly and alone, afraid to seek help, ashamed of what others may think. Too many outsiders are quick to make assumptions, mislabeling people as inherently bad without looking beyond the surface.

Earlier this year, I met a heroin dealer who attempted to take his own life days earlier. He was living with post-traumatic stress disorder and major depression untreated for several years. As a teenager, he sustained a gunshot wound to the jaw during a drug-deal-gone-wrong. It was a miracle that he survived, except the memory of what happened left him crippled with fear every time he left the house. He tried to hold down normal jobs, but ultimately returned to dealing heroin. He hated his clients, was constantly haunted by a feeling of distrust, and felt deep guilt for supplying others with a deadly drug. But it was the only job that could pay his daughter’s medical bills. Dealing heroin enabled him to pay for the surgeries she needed. He moved his family out of the hood and into a neighboring suburb, allowing his children to transfer to a better school district and feel safe playing in the yard. “For my kids, I’d do anything. Wouldn’t you?” He asked.

Everyone has a story, a reason why, a fight we cannot see. Substance users are people, just like you and me. Their identities extend far beyond addiction; they should not be defined by their illness. As a community, we must learn to give others grace, the chance to explain, the benefit of the doubt – for the hardest battles are often invisible.